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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/529,937 | 06/30/2000 | MARIA EUGENIA MEIRINHOS DA CRUZ | 249-119P | 2705 |

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| EXAMINER | |
|---|---|
| KISHORE, GOLLAMUDI S | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1615 | |

DATE MAILED: 03/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/529,937 | MEIRINHOS DA CRUZ ET AL. | |
| | Examiner | Art Unit | |
| | Gollamudi S Kishore, PhD | 1615 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☐ Responsive to communication(s) filed on *22 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *23-25 and 27-42* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23-25 and 27-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. §§ 119 and 120**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

The filing of an RCE, amendment and declaration dated 1-22-04 are acknowledged.

Claims included in the prosecution are 23-25 and 27-42.

### *Claim Rejections - 35 USC § 112*

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 40 and 41 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 40 is confusing. Is it drawn to a method of administration or method of treatment? The claim recites 'applying'; it is unclear as to in what way it is applied. Is it external? Also unclear is what the humans and animals are treated for. Clarification is requested.

According to claim 25, the preparation is a final preparation and it is unclear what applicant is intending to convey through claim 41. The claim recites, "method of preparation of a pharmaceutical composition"; yet recites no distinct additional steps from the process of claim 25. Furthermore, as pointed out above, it is unclear as to what the humans or animals are treated for. The term, 'therapeutic quantity' does not have meaning if the disease to be treated is not recited.

*Claim Rejections - 35 U.S.C. § 102*

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 23-24, 39 and 41are rejected under 35 U.S.C. 102(b) as being anticipated by WO 95/31970 of record.

WO discloses liposomal formulations containing trifluralin; the liposomes are made of phosphatidylcholine. Since the process of preparation in the prior art results in a liposome population of different sizes, the reference meets the requirements of dependent claims (note the abstract and claims). It should be noted that product by process claims are still deemed to be product claims, in the absence of showing that the product is patentably distinct from the prior art product.

*Claim Rejections - 35 U.S.C. § 103*

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the

subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 23-24 and 39-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over applicant's statements of prior art in view of Steck (4,186,183), Rao (4,594,241) individually or in combination or vice versa (Steck or Rao in view of applicant's statements of prior art).

Applicant in the paragraph bridging pages 3 and 4 of the specification indicate that the herbicide, trifluralin is a well-known anti-leishmania drug.

Steck teaches liposomal carriers for the treatment of leishmaniasis (note the abstract). According to Steck the liposomes are taken up rapidly by cells and intra-cellular lysosomes of the reticuloendothelial system and that the characteristics of liposomes suggested that they might have a potential for application of carriers for anti-leishmania agents. Steck also teaches that the cells and tissues in which the liposomes are readily taken up are the very locations in which the Leishmania organisms predominantly reside (note col. 2, lines 6-26). The anti-leishmania drug taught by Steck however, is not the claimed drug.

Rao similarly teaches the effectiveness of the liposomally encapsulated anti-leishmania drugs against this organism (note the abstract, examples and claims). The anti-leishmania drug taught by Rao however, is not the claimed compound.

The use of the liposomes as carriers of trifluralin would have been obvious to one of ordinary skill in the art because of effectiveness of liposomes as carriers of anti-leishmania drugs taught by Steck and Rao. Alternately, the use of trifluralin in the liposomes of Steck or Rao would have been obvious to one of ordinary skill in the art with the expectation of obtaining the benefits of the liposomes since trifluralin is an art known anti-leishmania drug.

7. Claims 25, 27-39 and 41-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over applicant's statements of prior art in view of Steck (4,186,183), Rao (4,594,241) individually or in combination or vice versa as set forth above, further in view of GB 2 002 319.

The method of preparation of liposomes by Steck involves hydration of the lipid film with an aqueous medium and shaking by a vortex mixer (examples). Rao's preparation of liposomes involves a similar procedure (examples). What are lacking in Steck, and Rao are the teachings of preparation of different sizes of liposomes and mixing them. It should be pointed out however, that by the hydration of lipid film, liposomes of different sizes are produced. The reference of Ryman and Tyrrell is cited of interest in this context (see page 51). Therefore, in the absence of showing unexpected results, mixing different populations of liposomes after sizing them by art known extrusion process or preparation of liposomes of different populations of liposomes by the conventional hydration process are deemed to be obvious manipulations practiced by an artisan. Steck, and Rao are also lack the teachings of the dehydration of the liposomes and hydrating them again when needed.

GB teaches that liposomes can be dehydrated for storage as a stable powder. According to GB such dehydrated powders can be stored for long periods and from which a dispersion of liposomes can be reconstituted (note the abstract).

Dehydrating the liposomes of Steck or Rao would have been obvious to one of ordinary skill in the art because GB teaches that the liposomal powders can be stored for a long time.

The declaration filed under 37 C.F.R. 1.132 has been carefully reviewed; it is not found to be persuasive. During the interview, the examiner had suggested the addition of size ranges and the percent ratios and to submit data showing unexpected results. The experimental data submitted does not appear to show the criticality of the sizes of the liposomes. The results reported in Table 1 shows only comparison of different result obtained using different lipids and Table 1 shows the apparent single dose toxicity dose of TFL.

Applicant's previous arguments have been addressed extensively before. Applicant has not provided any additional arguments and therefore, the rejections are maintained.

The reference of Deamer, which shows that the sizing of the liposomes by extrusion is known in the art, is cited of interest.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gollamudi S Kishore, PhD whose telephone number is (571) 272-0598. The examiner can normally be reached on 6:30 AM- 4 PM, alternate Friday off.

[redacted]

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman K Page can be reached on (571) 272-0602. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 308 1234.

Gollamudi S Kishore, PhD
Primary Examiner
Art Unit 1615

GSK